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Mapping transcriptome profiles of *in vitro* iPSC-derived cardiac differentiation to *in utero* heart development

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ABSTRACT

The dataset includes microarray data (Affymetrix Mouse Genome 430 2.0 Array) from WT and Nos3$^{-/-}$ mouse embryonic heart ventricular tissues at 14.5 days post coitum (E14.5), induced pluripotent stem cells (iPSCs) derived from WT and Nos3$^{-/-}$ mouse tail tip fibroblasts, iPSC-differentiated cardiomyocytes at Day 11, and mouse embryonic stem cells (mESCs) and differentiated cardiomyocytes as positive controls for mouse iPSC differentiation. Both *in utero* (using embryonic heart tissues) and *in vitro* (using iPSCs and differentiated cells) microarray datasets were deposited to the NCBI Gene Expression Omnibus (GEO) database. The deposited data in GEO include raw microarray data, metadata for sample source information, experimental design, sample and data processing, and gene expression matrix. The data are available under GEO Access Number GSE69317 (GSE69315 for tissue sample microarray data, GSE69316 for iPSCs microarray data, http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc= GSE69317).

Specifications	
Organism/cell line/tissue	*Mus musculus* (*mouse*)/*Nos3*$^{-/-}$ *mouse tail tip-derived iPSCs and iPSC-derived cardiomyocytes/Nos3*$^{-/-}$ (*B6.129P2-Nos3tm1unc/J, The Jackson Laboratory, Bar Harbor, ME*) *and wild type* (*WT*) *CD1* (*Harlan Laboratories, Indianapolis, IN*) *mouse heart tissues* (*left and right ventricular tissues, or LV and RV*) *at 14.5 days post coitum* (*E14.5*)
Sex	*Male mice for iPSCs*
Sequencer or array type	*GPL1261/*[*Mouse430_2*] *Affymetrix Mouse Genome 430 2.0 Array*
Data format	*Raw microarray data* (*.CEL files*) *and computed gene expression matrix using RMA*
Experimental factors	*WT LV vs.* Nos3$^{-/-}$ *LV*; *WT RV vs.* Nos3$^{-/-}$ *RV*; *WT iPSCs vs.* Nos3$^{-/-}$ *iPSCs*; *WT iPSC-differentiated cardiomyocytes at D11 vs.* Nos3$^{-/-}$ *iPSC-differentiated cardiomyocytes*
Experimental features	*The experiments are designed to compare the transcriptome profiles of embryonic heart tissues* (*LV and RV*) *between WT and* Nos3$^{-/-}$ *mice* (*in utero comparison*). *The transcriptome profiles of iPSCs derived from both WT and* Nos3$^{-/-}$ *mice tail tip fibroblasts and their differentiated cardiomyocytes are also compared in this study.*
Consent	*N/A*
Sample source location	*Nos3*$^{-/-}$ (*B6.129P2-Nos3tm1unc/J, The Jackson Laboratory, Bar Harbor, ME*) *and wild type* (*WT*) *CD1* (*Harlan Laboratories, Indianapolis, IN*)

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1. Direct link to deposited data

http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE69317.
Series GSE69317.

2. Experimental design, materials and methods

The experimental design of this study is to model the Nos3-related cardiac defects using an induced pluripotent stem cell (iPSC) platform and investigate the underlying disease pathogenesis by mapping the transcriptome profiles using tail tip derived iPSCs of wild type (WT) CD1 (Harlan Laboratories, Indianapolis, IN) and Nos3 −/− (B6.129P2-Nos3tm1unc/J, The Jackson Laboratory, Bar Harbor, ME) mice back to the gene expression profiles of corresponding embryonic heart tissues.

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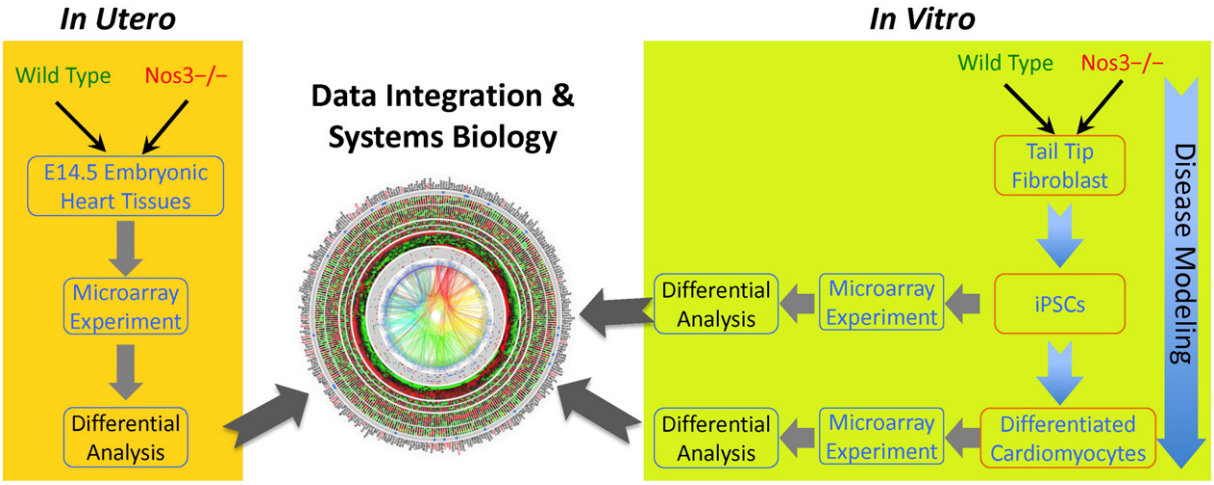

Fig. 1. Overall strategy of study design and data analysis. Transcriptome profiling using microarray was performed on embryonic heart tissues (*in utero*, left orange box). *In vitro* disease modeling for Nos3-related cardiac defects was conducted using induced pluripotent stem cells (iPSCs) derived from fibroblast (right green box). Microarray experiments were performed on both iPSCs and differentiated cardiomyocytes. Systems biology study integrated both *in utero* and in *vitro* transcriptome information to pinpoint the disease associated genes and networks (central circular plot).

In utero microarray experiments used WT mouse embryonic heart tissues as a gold standard. In brief, WT and Nos3 −/− embryos were harvested at 14.5 days post coitum (E14.5) and dissected for embryonic heart tissues. Biological triplicate samples were collected for microarray experiments with each sample containing tissues from 15 to 30 embryos. To accurately profile the transcriptomes in different heart chambers, left and right ventricular tissues (LV and RV) were microdissected for RNA extraction. For *in vitro* microarray experiments, tail tip fibroblasts were harvested from the distal part of the tail of WT and Nos3 −/− adult male mice. After culturing for 1–2 weeks in Dulbecco's modified Eagle's medium (DMEM, Life Technologies, Grand Island, NY), tail tip fibroblasts were infected with viral vectors from the CytoTuneTM-iPS 2.0 Sendai Reprogramming Kit (Life Technologies, Grand Island, NY). Sendai viral vectors encoding hKOS (hKlf4, hOct4, hSox2), hcMyc, and hKlf4 were introduced at multiplicities of infection of 5:5:3, respectively. The detailed process is published in the original paper [1]. Emerging WT and Nos3 −/− iPSC colonies were harvested for RNA extraction and microarray analysis. To model the Nos3-related heart defects *in vitro*, WT and Nos3 −/− iPSCs were spontaneously differentiated into beating cardiomyocytes and allowed to expand until Day 11 of differentiation with medium refreshed every other day. Differentiated cardiomyocytes were identified by beating activity and expression of α-actinin. In addition, mouse embryonic stem cells (mESCs; R1, G4, CGR8) were used as additional quality controls for *in vitro* cardiac differentiation.

RNA from embryonic tissue samples, iPSCs, and differentiated cardiomyocytes was extracted with the RNeasy kit (Qiagen, Germantown, MD) for microarray experiments. GeneChip Mouse Genome 430 2.0 Arrays (Affymetrix, Santa Clara, CA) were used to profile the transcriptome in both tissue and cell line samples. Stringent quality assessment and quality control procedures were performed in this study, which are described in our previous publication [2]. According to standard Affymetrix microarray protocol, Biotinylated complementary RNA (cRNA) was prepared from 100 ng total RNA. Following fragmentation, 10 μg of cRNA was hybridized for 16 h at 45 °C on the microarray. GeneChips were washed and stained in the Affymetrix Fluidics Station 450 and then scanned using the GeneChip Scanner 3000 7G.

Microarray data was normalized and processed using the RMA method [3,4] to calculate the gene expression matrix. The differential analysis was performed using the LIMMA method [5]. Pairwise differential analyses were performed between the following groups: WT LV vs. Nos3 −/− LV, WT RV vs. Nos3 −/− RV, WT iPSCs vs. Nos3 −/− iPSCs, WT iPSC-derived cardiomyocytes vs. Nos3 −/− iPSC-derived cardiomyocytes (Fig. 1). Mouse ESC and ESC-derived cardiomyocytes were used as positive controls in clustering and PCA analyses. Following differential analysis, a systems biology strategy was applied to integrate differential genes from both *in utero* and *in vitro* microarray experiments along with gene interaction information to pinpoint the concordant genes and network hubs.

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